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Preface

We would like to present, with great pleasure, the inaugural volume-6, Issue-8, August 2020, of a scholarly journal, *International Multispeciality Journal of Health*. This journal is part of the AD Publications series *in the field of Medical, Health and Pharmaceutical Research Development*, and is devoted to the gamut of Medical, Health and Pharmaceutical issues, from theoretical aspects to application-dependent studies and the validation of emerging technologies.

This journal was envisioned and founded to represent the growing needs of Medical, Health and Pharmaceutical as an emerging and increasingly vital field, now widely recognized as an integral part of scientific and technical statistics investigations. Its mission is to become a voice of the Medical, Health and Pharmaceutical community, addressing researchers and practitioners in below areas

Clinical Specialty and Super-specialty Medical Science:

It includes articles related to General Medicine, General Surgery, Gynecology & Obstetrics, Pediatrics, Anesthesia, Ophthalmology, Orthopedics, Otorhinolaryngology (ENT), Physical Medicine & Rehabilitation, Dermatology & Venereology, Psychiatry, Radio Diagnosis, Cardiology Medicine, Cardiothoracic Surgery, Neurology Medicine, Neurosurgery, Pediatric Surgery, Plastic Surgery, Gastroentrology, Gastrointestinal Surgery, Pulmonary Medicine, Immunology & Immunogenetics, Transfusion Medicine (Blood Bank), Hematology, Biomedical Engineering, Biophysics, Biostatistics, Biotechnology, Health Administration, Health Planning and Management, Hospital Management, Nephrology, Urology, Endocrinology, Reproductive Biology, Radiotherapy, Oncology and Geriatric Medicine.

Para-clinical Medical Science:

It includes articles related to Pathology, Microbiology, Forensic Medicine and Toxicology, Community Medicine and Pharmacology.

Basic Medical Science:

It includes articles related to Anatomy, Physiology and Biochemistry.

Spiritual Health Science:

It includes articles related to Yoga, Meditation, Pranayam and Chakra-healing.

Each article in this issue provides an example of a concrete industrial application or a case study of the presented methodology to amplify the impact of the contribution. We are very thankful to everybody within

that community who supported the idea of creating a new Research with *IMJ Health*. We are certain that this issue will be followed by many others, reporting new developments in the Medical, Health and Pharmaceutical Research Science field. This issue would not have been possible without the great support of the Reviewer, Editorial Board members and also with our Advisory Board Members, and we would like to express our sincere thanks to all of them. We would also like to express our gratitude to the editorial staff of AD Publications, who supported us at every stage of the project. It is our hope that this fine collection of articles will be a valuable resource for *IMJ Health* readers and will stimulate further research into the vibrant area of Medical, Health and Pharmaceutical Research.

Dr. Kusum Gaur
(Chief Editor)

Mr. Mukesh Arora
(Managing Editor)

Board Members

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Dr. Kusum Gaur working as professor Community Medicine and member of Research Review Board of Sawai Man Singh Medical College, Jaipur (Raj) India.

She has awarded with WHO Fellowship for IEC at Bangkok. She has done management course from NIHFW. She has published and present many research paper in India as well as abroad in the field of community medicine and medical education. She has developed Socio-economic Status Scale (Gaur's SES) and Spiritual Health Assessment Scale (SHAS). She is 1st author of a book entitled " Community Medicine: Practical Guide and Logbook.

Research Area: Community Medicine, Biostatics, Epidemiology, Health and Hospital Management and Spiritual Health.

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Research Area: Community Mental Health, Psycho somatic and liaison Psychiatry.

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Dr. Lokendra Sharma is Associate Professor Pharmacology and working as Nodal officer of SMS Medical College, Jaipur.

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Dr. Rajeev Yadav is working as Associate Professor Community Medicine, SMS Medical College, Jaipur (Rajsthan) India. He is member of Research Review Board of the Institute.

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Dr. Praveen Mathur is working as Professor- Pediatric Surgery and is recipient of Commonwealth Fellowship in Pediatric Laparoscopy from Uk and fellowship award in minimal access Surgery (FMAS). He has done Clinical observer ship in the Department of Pediatric Surgery, Johns Hopkins University, Baltimore, USA. (2008). He has presented and published a number of research articles at national and international level. He is reviewer of prestigious Journal of Pediatric Surgery (JPS) and World Journal of Gastroenterology, Journal of neonatal Surgery (JNS).

Research Area: Pediatric Surgery & Laparoscopy.

Dr. Lokendra Sharma

Dr. Lokendra Sharma is Associate Professor Pharmacology and working as Nodal officer of SMS Medical College, Jaipur.

He is recipient of WHO Fellowship award on Poison Patient Management at Vietnam. He is resource faculty for Experimental Toxicology and Basic Course for Medical Education. He is presented and published a lot of research articles at national and international level.

Research Area: PHARMACOLOGY.

Dr Rajeev Sharma (MS; FMAS; FIMSA;FCLS)

He is working as Professor, Department of Surgery, Government Medical College, Chandigarh, India. He has done FMAS, FIMSA and FCLS along with MS (Gen Surgery).

He has about 50 international and national publications to his credit. He has held various positions in the Association of Minimal Access Surgeons of India (AMASI) from time to time. He has also acted as instructor of various AMASI skill courses held at different places in India. He has established Surgical Technique learning centre at GMCH Chandigarh for imparting training to the budding surgeons in the field of minimal access surgery. He is also the reviewer in the subject in various journals.

Research Area: Minimal Access Surgery.

Dr Anshu Sharma (MS ANATOMY)

She is Presently working as assistant professor in the department of Anatomy, GMCH, Chandigarh. She has many publications in various national and international journals. She is executive member of Anatomical Society of India (ASI) and North Chapter of ASI. She is also a member of editorial board of Journal of Medical College Chandigarh.

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He has authored a book entitled "Community Medicine: Practical Guide and Logbook".

Research Area: His areas of Interest are Epidemiology, Biostatistics and Spiritual Health.

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Dr. Virendra Singh worked as Supernatant and head of department of Pulmonary Medicine, SMS Medical College, Jaipur (Rajsthan) India.

He has gone abroad for many training courses and to present research papers. He had been chairman of Research Review Board of SMS Medical College, Jaipur. He is a great research scholar and had published book related to his faculty and had many publications in indexed journals.

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Dr. Mahesh Sharma is a Principle specialist General Surgery in Rajasthan State Government, India. He has been PMO of district hospitals for more than 15 years. He has gone abroad as observer of many of training related to his speciality. He has published and present many research paper in India as well as abroad.
He has developed Spiritual Health Assessment Scale (SHAS) with Dr. Kusum Gaur.

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Dr. Praveen Mathur

Dr. Praveen Mathur is working as Professor- Pediatric Surgery and is recipient of Commonwealth Fellowship in Pediatric Laparoscopy from Uk and fellowship award in minimal access Surgery (FMAS). He has done Clinical observer ship in the Department of Pediatric Surgery, Johns Hopkins University, Baltimore, USA. (2008). He has presented and published a number of research articles at national and international level. He is reviewer of prestigious Journal of Pediatric Surgery (JPS) and World Journal of Gastroenterology, Journal of neonatal Surgery (JNS).

Research Area: Pediatric Surgery & Laparoscopy.

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Management of Sepsis Patient Aggravated by Diabetic Ketoacidosis

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Abstract**—** *Sepsis is a life-threatening organ dysfunction caused by dysregulation of the host's response to infection. Sepsis can lead to ketoacidosis in diabetes mellitus patients. A 60 years old male complained of headache, mild fever and painful swallowing since 2 weeks prior to hospital admission. History of diabetes mellitus is unknown. Based on examination, the working diagnosis for the patient was sepsis, suspected periapical abscess, type II diabetes mellitus with diabetic ketoacidosis and decreased consciousness. Initial management of sepsis, insulin, and endotracheal intubation were performed. The patient then was admitted to the ICU. Management of sepsis is very important and should be performed based on 1-hour SSC bundle while performing management of DKA. The patient had periapical abscess which is thought to be the source of sepsis. Sepsis then triggers DKA, and several organ dysfunctions in the form of AKI, DIC, and respiratory distress.*

Keywords— Diabetic ketoacidosis, Periapical abscess, Sepsis.

I. INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by dysregulation of the host's response to infection. Organ dysfunction is identified using the Sequential Organ Failure Assessment score (SOFA score). SOFA score equal to or more than 2 reflect a risk of death of around 10%. This requires prompt and appropriate intervention so that the condition does not get worse[1].

Sepsis can lead to ketoacidosis in diabetes mellitus patients. More than 50% of KAD cases are thought to be triggered by infection. Diabetic ketoacidosis is an acute metabolic disorder characterized by increasing circulating ketone bodies which progresses to ketoacidosis with uncontrolled hyperglycemia due to insulin deficiency. Acidic ketone bodies are produced by lipolysis process. Acidosis occurs when ketone levels exceed the body's buffer capacity. During an infection there will be an increase in the secretion of cortisol and glucagon hence there is a significant increase in blood sugar levels[1].

II. CASE PRESENTATION

60 years old male, complained of headache, not too high body temperature and painful swallowing since 2 weeks before hospital admission and He received antibiotics for a week from an ENT doctor. Three days before hospital admission, the patient experienced decrease in consciousness, slept more often but awoken when called. There are no seizures, vomiting, numbness and weakness of the limbs. The patient also has no history of stroke.

The patient was taken to Hospital B and treated there. During treatment, it was found that there was a tooth infection and an increase in blood sugar levels. The history of diabetes in the patient is unknown, but the family (father, brother and sister) is known to have diabetes. The patient was then referred to RSHS. On examination at the emergency room, it was obtained that the patient has GCS of 9

(E2M5V2), blood pressure 111/67 mmHg (MAP 81 mmHg), pulse rate 127 x/m, respiratory rate 40 x/m with saturation 99% using O2 5 L/m via binasal cannula, and temperature of 37o C. On the Chest examination, it was found that the patient has regular heart sounds, VBS in both lung fields. Normal abdominal examination. On neurological examination, during meningeal stimulation it was found that the patient has stiff neck (+), no resistance on laseque/kernig, brudzinski I/II/III/IV (-). No other neurological deficits were found.

From the laboratory test it was obtained that Hb 14.6 g/dl, Ht 41.8%, Leukocytes 17,870/uL, platelets 49,000/uL, PT 10.20, aPTT 29.10, INR 0.90, Blood Sugar 343 mg/dl, SGOT 31, SGPT 51, total bilirubin 0.290, indirect bilirubin 0.443, Albumin 1.8, Ureum 43 mg/dL, Creatinine 0.93 mg/dl, Na 150 mEq/L, K 3.6 mEq/L, Cl 124 mEq/L, Ca 5.2 mg/dL, Mg 2,2 mg/dL, Fibrinogen 620 mg/dL, D-dimer 5.10 mcg/mL, pH 7.00, pCO2 27.4, pO2 144.4, HCO3 6.8, BE -22 , 5, SpO2 97.5, Lactate 0.9, Urine ketones +3. Radiological abnormalities were not seen on chest and lung radiographs. Panoramic: dental caries on tooth 17, periapical abscess.

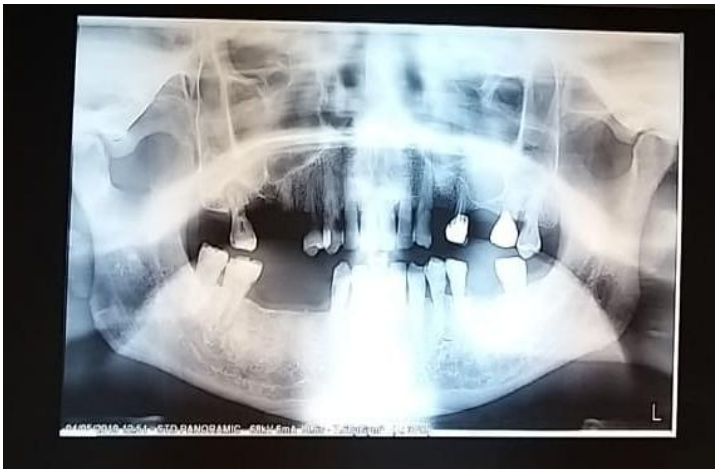


FIGURE 1: Panoramic

Based on this examination, the patient met the criteria for sepsis (SOFA score> 2), which was obtained from the respiratory examination with a PF Ratio of 144.4: 0.41 = 352 (1), platelets of 49,000/uL (3) and GCS of 9 (3) making the total of this patient's SOFA score 7.

Table 1. Sequential Organ Failure Assessment Score

Variables	SOFA Score				
	0	1	2	3	4
Respiratory	PaO_2/FiO_2: > 400 SpO_2/FiO_2: > 302	PaO_2/FiO_2: < 400 SpO_2/FiO_2: < 302	PaO_2/FiO_2: < 300 SpO_2/FiO_2: < 221	PaO_2/FiO_2: < 200 SpO_2/FiO_2: < 142	PaO_2/FiO_2: < 100 SpO_2/FiO_2: < 67
Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP < 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 or Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (bilirubin, mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12
Renal (creatinine, mg/dL)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Coagulation (platelets x $10^3/mm^3$)	≥ 150	< 150	< 100	< 50	< 20
Neurologic (GCS score)	15	13-14	10-12	6-9	< 6

According to Sepsis-3, a new (or presumed new) increase in SOFA score above baseline in the presence of infection makes the diagnosis of sepsis. Increasing SOFA scores are associated with incremental increases in mortality.

Abbreviations: GCS, Glasgow coma scale; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, arterial oxygen pressure; SOFA, sequential organ failure assessment (score); SpO_2, oxygen saturation.

FIGURE 2: SOFA Score

The working diagnosis are sepsis, suspected periapical abscess, type II diabetes mellitus with diabetic ketoacidosis, decreased consciousness e.c. metabolic (sepsis and KAD) DD/ e.c. suspected bacterial meningitis, respiratory failure.

Initial management of sepsis according to the recommendations of the Surviving Sepsis Campaign (SSC) is administering crystalloid (RL) 30 ml/kg intravenously, performing blood culture, and administration of antibiotics. Insulin 0.5 U/hour was given. Endotracheal intubation was performed in this patient due to signs of respiratory failure (RR of 40 x/m) and metabolic acidosis in this patient was not well compensated by the patient's respiratory system. The patient was subsequently admitted to the ICU.

III. CARE IN THE ICU

Patient's condition on ICU admission was GCS 6T (E3M3VT), Blood Pressure 110/70 mmHg, HR 120 x/m, Temperature 36oC, Respiration: Ventilator SIMV mode, RR 12 x/m, PC 12, PEEP 5, FiO2 50%, RR actual 12–30 x / m, SpO2 98%. Diuresis 400-500 cc/hour.

Echohemodynamic results: CO: 5.1 L/minute, CI: 3.1 l/minute, SVR: 910 dynes sec cm-5, Distansibility index: 75%, fluid responsiveness (+).

Patient assessment on admission: Sepsis e.c. suspected periapical abscess, type II diabetes mellitus with Diabetic Ketoacidosis, decreased consciousness e.c. metabolic (sepsis and KAD) DD/ e.c. suspected bacterial meningitis, Respiratory Failure.

The treatment plan is aimed at fluid rehydration continuation, overcoming infection and sepsis with antibiotics and source control; management of KAD with administration of fluids, insulin, and electrolyte correction. For respiratory support with ventilator;

The patient was given loading of crystalloid fluid (RL) 300 cc in 1 hour followed by maintenance 2000 cc/24 hours, plasmanate 50 cc/hour, insulin 0.5 - 2 U/hour.

The patient was given meropenem 3 x 1 gr, levofloxacin 1 x 750 mg, ceftazidim 3 x 2 gr, and metronidazole 1 x 1500 mg. In addition, 8 mg/hour of esomeprazole and Paracetamol 4 x 1 gr was also given.

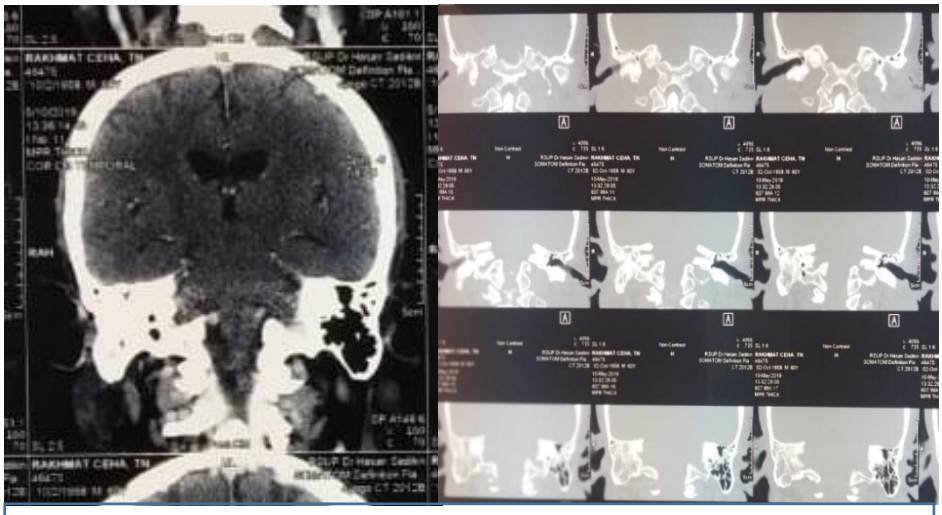
On day 1 in the ICU, the patient's GCS was 6T (E3M3VT), Blood pressure 122/78 mmHg, HR 88-90 x/m, temperature 36.6 0C, CVP 9-11 mmHg, respiration with ventilator mode PS 12, PEEP 6, FiO2 45% with RR of 20-28 x/m, TV 480-520 ml, SpO2 99-100%, Diuresis 200-300-100 cc/hour, Balance: -110/24 hours. Echodynamics: kissing LV with IVC colaps > 50%, fluid responsiveness (+). LVEF 76%, global normokinetics, normal valves, SVR 1040 dyne.s.cm-5. In laboratory examination, there was an increase in creatinine > 1.5 times the baseline, thus it met the criteria for stage 1 AKI (KDIGO).

On day 2 of treatment, on the ENT examination it was found the presence of acute otitis media at the stage of the perforation of the right auricle and a plan to do a temporal CT scan with axial coronal section and aural toilet. Source control action by oral surgeon was performed by extracting tooth 17. On this day, there was also an increase in lactate to 3.7.

During the ICU stay, the patient's hemodynamic was relatively stable without the use of support. The level of conciousness and respiration also showed some improvement. The clinical condition continued to improve after source control measures and hemodialysis measures indicated for sepsis.

TABLE 1
LABORATORY RESULTS DURING TREATMENT IN THE ICU

Laboratory result	Day 0 6/5	Day 1 7/5	Day 2 8/5	Day 3 9/5	Day 4 10/5	Day 5 11/5	Day 6 12/5	Day 7 13/5	Day 8 14/5
Hb	14,6	12,7	14,2	12	12,5	11,2	10,3	9,4	9,2
Ht	41,8	34	37,9	31,9	34,6	31,5	28,5	26,5	26,5
Leucocyte	17870	10240	10,700	8230	10500	9770	10200	8540	8430
Platelet	49000	55000	90000	96000	122000	99000	115000	126000	185000
PT	10,20			12,9	13,5				
aPTT	29,0			22,60	22,7				
INR	0,9			1,16	1,22				
Fibrinogen	620				212,4				
D-Dimer	5,10				3,97				
Blood Glucose	343	248	268/248/219	322	172		155	187	
Urine ketone	+3								
Lactate	0.9		3,7		1,5			1,2	
Natrium	150	154	156/161	156	154	141	143		140
Kalium	3,6	2,4	3,3/ 3,3	2,5	2,4	4,1	3,2		3,9
Chloride	124	124	121	117	113	102	107		
Calsium	5,2	4,09	4,73/4,98	4,13	4,46	4,36	4,74		4,87
Magnesium	2,2	2,0		1,9	1,8	1,4	1,8		1,4
Ureum	43	62	62	75,9	59,1	45	40	43	45
Creatinine	0,93	1,55	1,55	1,74	1,46	1,2	1,06	1,15	1,2
pH	7.00	7,346	7,396	7,47	7,532	7,430	7,439		7,452
pCO2	27,4	19,6	19,0	32	29,1	31,9	38,1		35,5
pO2	144	184	124,0	47,3	134,7	222	212,4		125,2
HCO3	6,8	10,8	11,8	23	24,6	21,4	26		25,1
BE	-22.5	-12,2	-10,2		2,7	-1,9	2,5		1,9
SatO2	97,5	99,7	99,0	84,2	98,3	98,6	99,6		98,2
Albumin	2,1	2,1	2,1		1,89				
SGOT	31								
SGPT	51								
Total Bilirubin	0,733								
Direct Bilirubin	0,290								
Indirect Bilirubin	0,443								
Urine/24 hour	Urine Na 144,7 mmol/L Urine volume 6800 ml/24 hour Urine NA calc 984,0 mmol/24 hour								



- Right
- Bilateral sphenoid sinusitis
- There were no signs of meningitis, intracranial bleeding, ischemic lesions, SOL / neoplasms and vascular malformations.

FIGURE 3: Temporal CT Scan

IV. DISCUSSION

Bacterial meningitis is a medical emergency with significant morbidity and mortality, requiring immediate recognition and immediate treatment. In bacterial meningitis there is inflammation of the meninges, especially arachnoid and piamater, due to bacterial invasion in the subarachnoid space. Meningitis is a syndrome consistent with the classic triad of fever, headache and meningismus. Patients usually present with two out of three symptoms and a possible change in mental status.[1,2,3] Acute bacterial meningitis occurs due to bacteria entering the bloodstream and migrate to the brain and spinal cord. Bacteria can also invade the meninges due to ear or sinus infections, skull base fractures, or after brain surgery. Diagnosis in this patient is based on complaints of headache, fever, decreased consciousness and the presence of neck stiffness on physical examination. The source of infection in this case was probably from dental infection with periapical abscess and ear infection with acute otitis media and sinusitis sphenoidalis[2-4].

Sepsis is a life-threatening organ dysfunction caused by dysregulation of the host's response to infection. Organ dysfunction can be identified as an acute change in total SOFA score (Sequential Organ Failure Assessment) $\geq$ 2 due to the presence of infection. The baseline SOFA score can be assumed to be zero in patients with no known previous organ dysfunction. A SOFA score of more than 2 reflects a risk of death of approximately 10%. This requires prompt and precise intervention so that a worsening condition does not occur[1].

Meanwhile, septic shock is a part of sepsis in which circulatory and cellular/metabolic disorders that underlie it can increase mortality. Patients with septic shock can be identified if there is sepsis accompanied with persistent hypotension requiring vasopressors to maintain MAP $\geq$ 65 mmHg and serum lactate levels > 2 mmol/L despite adequate fluid resuscitation.[4]

In this case the diagnosis of sepsis was based on impaired organ function in the form of respiratory distress (PaO2/FiO2= 144.4/0.4= 361), decreased consciousness GCS = 9 (E3, M3, V3), a hematological disorder in the form of thrombocytopenia (49,000/uL). SOFA score = 7.

Table 1. Sequential Organ Failure Assessment Score

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	0	1	2	3	4
Respiratory	PaO_2/FiO_2: > 400 SpO_2/FiO_2: > 302	PaO_2/FiO_2: < 400 SpO_2/FiO_2: < 302	PaO_2/FiO_2: < 300 SpO_2/FiO_2: < 221	PaO_2/FiO_2: < 200 SpO_2/FiO_2: < 142	PaO_2/FiO_2: < 100 SpO_2/FiO_2: < 67
Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP < 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 or Norepinephrine > 0.1 Phenylephrine > 0.8
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Abbreviations: GCS, Glasgow coma scale; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, arterial oxygen pressure; SOFA, sequential organ failure assessment (score); SpO_2, oxygen saturation.

FIGURE 4: SOFA score

Diabetic ketoacidosis (KAD) is a metabolic disorder caused by absolute or relative insulin deficiency, characterized by hyperglycemia, acidosis, and ketosis. KAD and Hyperosmolar Hyperglycemia State (HHS) are 2 serious and life-threatening complications of acute metabolic diabetes mellitus. Both of these conditions can occur in type 1 and type 2 diabetes mellitus (DM), but KAD is more common in type 1 diabetes.

Ketoacidosis is the result of a deficiency or ineffectiveness of insulin that occurs along with an increase in counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormones). This increased activity will break down triglycerides into glycerol and free fatty acids (FFA). Glycerol is an important substrate for gluconeogenesis in the liver, while the excessive production of free fatty acids is the main precursor of ketoacids. In the liver, free fatty acids are oxidized into ketones, which are mainly stimulated by glucagon.

Hyperglycemia occurs due to increased hepatic and renal glucose production (gluconeogenesis and glycogenolysis) and decreased glucose utilization in peripheral tissues. Hyperglycemia and high ketone levels cause osmotic diuresis which will result in hypovolemia and decreased glomerular filtration rate.

There are about 20% of KAD patients who are only known to have DM for the first time. The most common precipitating factor for KAD is infection, and it is estimated that it triggers more than 50% of cases of KAD. In infection there will be an increase in the secretion of cortisol and glucagon so that there is a significant increase in blood sugar levels. Other factors include cerebrovascular accidents, alcohol abuse, pancreatitis, heart infarction, trauma, pheochromocytoma, drugs, recently recognized type 1 diabetes and discontinuity (adherence) or inadequate insulin therapy.

Diagnosis of KAD in this patient was based on the finding of hyperglycemia conditions (GDS 343 mg/dl), acidosis conditions (Blood Gas Analysis: pH 7.00, pCO_2 27.4, pO_2 144.4, HCO_3 6.8, BE -22.5, $satO_2$ 97.5) and the presence of ketones in the urine (urine ketones +3). This condition is also supported by clinical conditions, namely: decreased consciousness (although the bias is caused by the patient's meningitis and sepsis conditions), Kussmaul's breathing, and tachycardia.

Dissaminated Intravascular Coagulation (DIC) is a condition in which bleeding and thrombosis occur. DIC is characterized by systemic activation of blood clots, which results in the formation and deposition of fibrin, which leads to microvascular thrombi in various organs and contributes to multiple organ dysfunction syndromes (MODS). DIC is a complication or effect of the development of another underlying disease and generally involves activation of systemic inflammation such as sepsis, trauma, organ destruction (such as pancreatysis), malignancy, severe transfusion reactions, obstetric complications, heatstroke.

Sepsis is a clinical syndrome defined as a systemic response to infection. It is often exacerbated by coagulopathy and by DIC in 35% of severe case. During sepsis, inflammation diffusely activates the coagulation system, consuming multiple blood clotting factors and producing DIC. In infection-induced SIRS, both disrupted endothelial cells and activated mononuclear cells produce proinflammatory cytokines that promote coagulation. In sepsis-associated DIC, antibiotics and treatment of the underlying disease are the main things in DIC therapy[1].

Acute Kidney Injury (AKI) is a serious complication that often occurs in critical illness. The incidence of AKI in patients hospitalized in the ICU is around 20 - 67%. Sepsis and septic shock are the main precipitating factors for AKI. AKI mortality rate in septic shock can reach 60%. Based on KDIGO criteria, AKI is diagnosed if the serum creatinine level increases by at least 0.3 mg/dL (26.5 µmol/L) in 48 hours or increases at least 1.5 times the baseline value in 7 days[1,5].

KDIGO Definition of AKI

AKI is defined as any of the following (*Not Graded*):

- Increase in SCr by ⩾0.3 mg/dl (⩾26.5 µmol/l) within 48 hours; or
- Increase in SCr to ⩾1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 ml/kg/h for 6 hours.

KDIGO AKI Staging

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

FIGURE 5. KDIGO

In this case, the diagnosis of AKI was based on an increase in creatinine levels. Initial creatinine on admission was 0.93 which increased within 24 hours to 1.55 (increase of more than 0.3 mg/dL or $\geq$ 1.5 times).

In this case, the mechanism of AKI formation can be caused by pre-renal (polyuri) and renal due to sepsis.

Stage 1 AKI management

- Stop drugs that are nephrotoxins

- Improve body fluid volume status:
  - Correction of hypovolemia, hydration, improve hemodynamics
  - Maintain MAP> 65 mmHg or SBP > 100 mmHg
  - Consider vasoactive use if hypotensive persists despite sufficient fluids.
  - Maintain a urine output of 0.5 ml / kg / hour

- Treatment of infection if present

- Manage and improve the risk factors that contribute to the disease.

V. PATIENT MANAGEMENT

The patient's problems stemmed from infection, presumably from periapical abscess of tooth 17, and acute otitis media of the right auricle. The causative bacteria infect the meninges through blood or direct invasion. The inflammatory reaction caused by this infection leads to sepsis which aggravates the general condition of the patient. Organ dysfunction that occurs includes thrombocytopenia and DIC, respiratory distress, and AKI. Sepsis also triggers KAD.

Therefore, the management of sepsis in this patient become is paramount, based on the hour-1 SSC Bundle:

1. Check the lactate level, recheck if the initial lactate level is > 2mmol/L
2. Take blood cultures before giving antibiotics.
3. Give broad spectrum antibiotics
4. Start giving 30 ml/kg body weight of crystalloid fluid immediately to patients with hypotension or lactate levels $\geq$ 4 mmol/L
5. Use vasopressors if hypotension is present during or after fluid resuscitation to maintain MAP $\geq$ 65 mmHg.

Management of patients in the emergency room was carried out following the h-1SSC.

DKA management targets:

1. Fluid resuscitation
2. Correction of acidosis and ketosis
3. Returning glucose levels to normal limits
4. Correction of electrolytes and fluid deficits
5. Identify and treat the causative factors

VI. CONCLUSION

In this case, a patient had a dental infection that progressed to periapical abscess, and acute otitis media with sphenoid sinusitis and mastoiditis. This is thought to be the source of spread of meningitis and sepsis. Sepsis then triggers KAD, and several organ disfunction in the form of AKI, DIC and respiratory distress.

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Functional Outcome of Diaphyseal Femoral Fractures Treated with Titanium Elastic Nail in Paediatric Age Group (05 To 15 Years)

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Abstract— *Femoral shaft fractures are very demanding injuries to the patients and their families. Majority of cases occurs in children and adolescents. Titanium elastic nailing is one of the operative procedures for treatment of such fractures. So this present study was conducted on 30 diaphyseal femoral fracture patients aged 05-15 years treated with Titanium elastic nailing with the aim to assess the functional outcome of such cases in western Rajasthan scenario. It was found that. average time of union was found 6.33 weeks, average period of full weight bearing was 7.66 weeks and with average time 6.4 weeks. So it conclude that fracture of femur treated with Titanium Elastic Nailing has very good results that Titanium Elastic Nailing is an ideal device to treat pediatric femoral shaft fractures between age group 5-15 years.*

Keywords: Femoral shaft fractures, diaphyseal femoral fracture, Titanium elastic nailing, Functional outcomes.

I. INTRODUCTION

Femoral shaft fractures are demanding and disabling injuries both to the patients and to the family. Peak incidence of this fracture occur at 2 & 17 years of age in a bimodal distribution and boys have a 2.6 times greater incidence than girls.[1]

The treatment of paediatric femoral shaft fractures depends on several factors age, fracture, pattern, and associated bone and soft tissue injuries. A variety of therapeutic alternatives such as external fixator, compression plating, rigid intramedullary nailing and elastic stable intramedullary nailing are being used for femoral shaft fractures in children. Operative treatment results in shorter hospitalization and early mobilization, which has psychological, social, educational and economic advantages over conservative treatment.

Flynn et al (2001)[2] stated that the ideal device to treat paediatric femoral shaft fractures would be a simple, load sharing internal splint allowing mobilization and maintenance of alignment for a few weeks until bridging callus forms. The device would also allow rapid healing and ability to remodel without risking the physis or blood supply to the femoral head. Flexible nailing meets the requirements of this ideal device (Flynn et al 2001).[7] Thus the aim to fix fractures of diaphysis of femur in children with intramedullary nails is to encourage formation of bridging periosteal callus.

Flexible nails is simple, safe, minimal invasive, appears to have few applications, does not interfere with growth and is associated with shorter hospital stay and rapid return to daily activities and school. It

avoids long and uncomfortable immobilization. Cosmetic damage is minimal, being limited to small scars at the sites of introduction of nails.[3]

So this study was conducted to find out the functional outcomes of femoral shaft fractures in children between 5-15 years of age and were treated by Titanium Elastic Nailing.

II. METHODOLOGY

This hospital based interventional study was conducted at Department of Orthopedics of SN Medical College & associated Hospital Mahatma Gandhi & Mathura Das Mathur Hospital, Jodhpur, Jodhpur (Rajasthan) India in 2018.

Before collecting the data, this study was approved by the institutional Ethics committee of SN Medical College, Jodhpur (Rajasthan) India and written informed consent was taken from every eligible subject.

For the study purpose, all patients with fracture shaft femur attended at orthopedic department of SN Medical College, Jodhpur were taken as study universe. Among them patients with 5-15 years having Diaphyseal close fractures and if compound then only corrected Gustilo's classification[4,5] type-I & type II was included in this study. Patients with segment fracture, very distal or very proximal fractures that precludes nail and patents who were unfit for surgery were excluded.

Patients who were eligible for study were operated and post operative protocol was follows as follows:-

- Antibiotic injection (Injection Cefotaxime 500mg - 1gm. was given at 2 pm, 10 pm and 9 am on the next day),
- One analgesic as and when required (Inj. Diclofenac 1-2 cc IM SOS),
- Dressing after 48 hours of surgery was done.
- Static quadriceps exercise was started 24 hours after the operation.
- Gentle knee bending exercise was started on 1st or 2nd postoperative day.
- Patient was discharged after 48-72 hours and called after 14 days for stitch removal.
- Patients were called for follow up after every 2 weeks upto two months and subsequently at monthly interval for six months.

Functional outcome of the patients in the form of weight bearing and rage of knee movement, were assessed after 6 month of follow-up.

Data thus collected were entered and compiled in MS Excel 2010 worksheet. These data were classified and analyzed as per objectives.

Statistical analysis: Qualitative data were expressed in percentage (%) and quantitative data were summarized as mean and standard deviation (S.D.).

III. RESULTS

In this present study, out of 30 study subjects, majority (22 i.e. 73.33%) were males and 8 (26.67%) were females with M:F ratio 2.75. The youngest patient was 5 years old and the eldest was 15 years old with an average age of 9.13 years. (Table 1)

TABLE 1
AGE AND SEX WISE DISTRIBUTION OF THE STUDY POPULATION (N=30)

S. No.	Variables		Number of subjects	Percentage
1	**Age group**	6-7 Years	6	20
		8-9 Years	7	23.3
		9-10 Years	11	**36.7**
		11-12 Years	2	6.7
		13-15 Years	4	13.3
2	**Sex**	Females	8	**73.33**
		Males	22	26.67

In present case series the most common site of fracture of shaft of femur was middle third 66.67% followed by distal third (13.3%) and upper third (20%). And the most common pattern of fracture was oblique fracture (50%) followed by transverse fractures (40%). (Table 2)

TABLE 2
FRACTURE CHARACTERISTICS WISE DISTRIBUTION OF THE STUDY POPULATION (N=30)

S. No.	Variables		Number of subjects	Percentage
1	**Site of Fracture**	Upper end	6	20
		Middle shaft	20	**66.7**
		Distal end	4	13.3
2	**Pattern of Fracture**	Transverse	12	40
		Oblique	15	**50**
		Other	3	10

Absence of pain on walking was taken as clinical indicator of union of fracture as per standard radiological and clinical criteria.[6] The average time of union was found 6.33 weeks. (Ranged between 6 8 wks). There was no case of delayed union and non union in present study. (Table 3)

Most of the patients started full weight bearing up to 8 weeks. The average period of full weight bearing was 7.66 weeks. (Table 3)

Majority of patients (86.67%) achieved full range of knee movement up to 6 weeks with average time 6.4 weeks. (Table 3)

TABLE 3
FUNCTIONAL OUTCOME OF THE STUDY POPULATION (N=30)

S. No.	Variables		Number of subjects	Percentage
1	**Time of Union**	6	25	**83.33**
		8	5	16.67
2	**Full weight bearing (weeks)**	6	6	20.0
		8	23	**76.7**
		10	1	3.3
		After 10	6	20.0
3	**Full range of knee movement (Weeks)**	6	26	**86.7**
		8	1	3.3
		9	2	6.7
		10	1	3.3

IV. DISCUSSION

In present study the most common site of fracture shaft femur was middle third 66.67% followed by distal third (13.3%) and upper third (20%). This proportion was almost equal to the proportion of site of fracture reported in study conducted by Flynn et al[7] and Cramer et al[8]. Flynn et al[7] also observed that the most common fracture of shaft of femur was middle third shaft femur fractures which was 72%. And likewise Cramer et al[8] also observed fracture of middle third shaft femur fractures in 70% among all fracture of shaft of femur.

In this present study the most common pattern of fracture was observed oblique fracture (50%) followed by transverse fractures (40%). This was contrast to the study conducted by Cramer et al[8] who found higher proportion of transverse pattern (60%) of fracture than other one. Even Mann et al[9] also reported higher proportion of transverse pattern (56%).

Average time of union was found 6.33 weeks in present study. Whereas it was reported more by other authors. Galpin et al[10] the average time of union was reported 9.1 weeks and Cramer et al[8] (2000) observed that all fractures were healed within 12 weeks. Literature[11] also reported that long bone takes 2-6 months to heal. This reason of lesser union time in present study may be because of better antibiotics and more facilities available nowadays.

In present study none of the cases was of delayed union and nonunion. Similar observations were of Flynn etall[7], Mann eatall[9], Cramer etall[8] and other studies[10-11.]

In present study, average time of full weight bearing was 7.66 weeks. Whereas other authors[7,9] reported more average time of full weight bearing than the present study. The average time of full weight bearing in study conducted by Flynn et al[7] was 8.5 weeks, while that in study conducted by Mann et al[9] it was 8.6 weeks. This reason of lesser average time of full weight bearing in present study may be because of better antibiotics and more facilities available nowadays.

V. CONCLUSION

This study conclude that fracture of femur treated with Titanium Elastic Nailing has very good results i.e. average time of union was found 6.33 weeks, average period of full weight bearing was 7.66 weeks and with average time 6.4 weeks. This concludes that Titanium Elastic Nailing is an ideal device to treat pediatric femoral shaft fractures between age group 5-15 years.

CONFLICT OF INTEREST

None declared till now.

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Design and Evaluation of Transdermal Patches of Labetalol Hydrochloride

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Abstract— *β-blockers like labetalol hydrochloride (LHCl) are potent and highly effective antihypertensive agents. The main drawback associated with β-blockers is extensive first-pass metabolism, variable bioavailability requiring frequent dose administration. This makes them an ideal candidate for transdermal therapeutic systems. β-blockers formulated as transdermal therapeutic system should enhance the bioavailability as well as improve patient compliance. Constant innovations and improvement in this field have potential that large-scale commercialization of transdermal dosage forms can be done.*

Aim: *The aim of the present work was to develop and evaluate matrix type transdermal patches containing new polymeric combination to enhance the bioavailability as well as improve patient compliance.*

Materials and Methods: *In present work development and evaluation of matrix-type transdermal patches containing a new polymeric combination of HPMC, carbopol934, ethyl cellulose, propylene glycol, polyethylene glycol, and isopropyl myristate for labetalol (LHCl) HCl (LBHCl). Film casting technique has been used in preparing patches. The patches were characterized for physical, in vitro release studies and ex vivo permeation studies using human cadaver skin.*

Result: *F_6 was found to be better than the other formulations and hence selected as the optimized formulation on the basis of results of evaluating parameters such as thickness, flatness, folding endurance, tensile strength, moisture content, moisture uptake, and drug content, formulation. The optimized patch was assessed for its pharmacokinetic, pharmacodynamic, skin irritation test and stability studies.*

Conclusion: *Successful development of sustained release matrix type of transdermal patches which can show greater patient compliance in treating hypertension has been done.*

Keywords— Drug delivery, labetalol hydrochloride, penetration enhancer, skin permeation, transdermal.

I. INTRODUCTION

Hypertension is usually defined by the presence of a chronic elevation of systemic arterial pressure above a certain threshold value. Hypertension is the most common cardiovascular disease worldwide. Its global occurrence is estimated to be around 1 billion individuals, and approximately 7.1 million deaths occur per year. Therefore, cost- effective approaches to optimally control blood pressure are need of the hour.

Management of hypertension with conventional dosage forms requires long-term treatment leading to poor patient compliance due to greater frequency of administration. Although there is the availability of

a plethora of therapeutically effective antihypertensive molecules, inadequate patient welfare is observed. It has provided a good platform for design and development of new formulations using different routes. Ever since the transdermal drug delivery has came into existence, it has offered great advantages including non-invasiveness, prolonged therapeutic effect, reduced side effects, improved bioavailability, better patient compliance, and easy termination of drug therapy. Attempts have been made to develop the transdermal therapeutic system for various antihypertensive agents, including β-blockers, an important antihypertensive class.[1-4]

The first-pass metabolism is a phenomenon, whereby the concentration of a drug is significantly reduced before it reaches the systemic circulation. One of the ways to avoid first-pass metabolism in case of antihypertensive drugs is formulating them in transdermal patch. The transdermal patch for labetalol hydrochloride (LHCl) can be prepared by different techniques using natural, semi-synthetic, and synthetic polymers.

A transdermal patch is a medicated adhesive patch that is positioned on the skin to transport a specific dose of medicine through the skin into the bloodstream. The major advantages provided by transdermal drug delivery system (TDDS) include enhanced bioavailability, more homogeneous plasma levels, longer duration of action leading to reduction in dose regularity, reduced side effects and enhanced therapeutic effect due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. TDDS avoid the GIT absorption and provide multi-day therapy with a single use, quick notification of medication in urgent situation and termination of drug therapy is rapidly possible through patch removal in case of side effects, can be easily applied and simply removed from the skin, it is the simple delivery system.[5-13]

Labetalol hydrochloride (LHCl) is an antihypertensive drug belonging to the class of β blockers. It has a low biological half-life of 2–5 h and undergoes extensive pre-systemic metabolism ranging from 14% to 89%. It has a low-molecular-weight (364.9), with no reported skin irritation history. It also has a favorable partition coefficient (7.08). With all these characteristics we propose LHCl to be an ideal drug candidate for the development of TDDS.[13-18]

II. MATERIALS AND METHODS

2.1 Chemicals and reagents

Chemicals and reagents for experimental work were procured as follows, LHCl was procured as gift samples from Cipla Ltd, HPMC procured from Loba Chemie, Mumbai, sodium lauryl sulfate and glycerine was procured from Merck, Mumbai, ethyl cellulose, dimethylsulfoxide, isopropyl myristate, and propylene glycol were procured from Molychem, Mumbai.

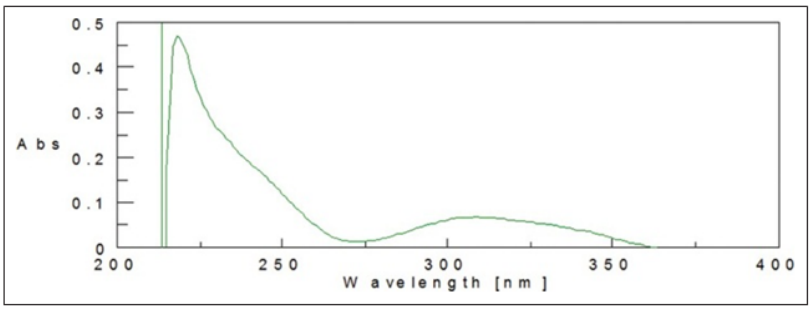
2.2 Experimental work

2.2.1 Validated analytical method development for determination of LHCl

2.2.1.1 Determination of λ max

The first important step in any analytical method development is a determination of λ max. Using this wavelength further validation has to be done. The result is presented in Figure 1.

FIGURE 1: Determination of λ max



2.2.1.2 Linearity

Several aliquots of LHCl hydrochloride were prepared separately at strength of 100 µg/ml, which were further diluted to prepare solutions in the concentration range of 2–10 µg/mL. Results of linearity, slope intercept, and correlation coefficient are shown in Tables 1 and 2, and Figure 2.

FIGURE 2: Calibration of labetalol hydrochloride

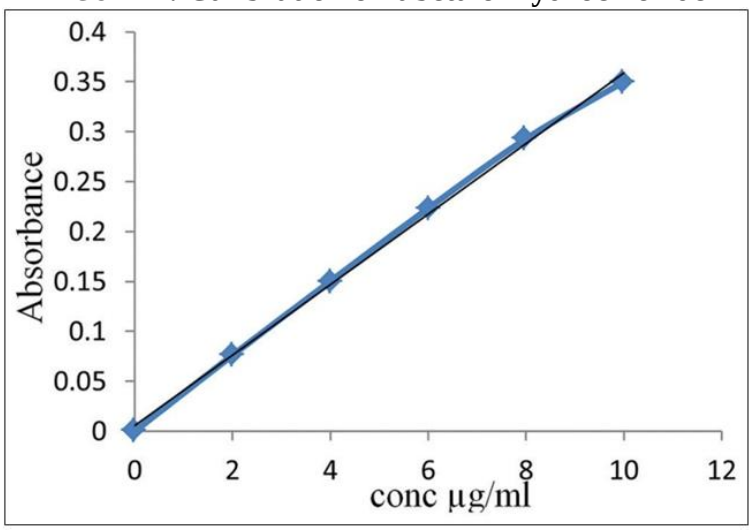


TABLE 1
RESULT OF LINEARITY RANGE

Concentration (µg/ml)	Absorbance
2	0.0762
4	0.1503
6	0.2233
8	0.2931
10	0.3502

TABLE 2
RESULT OF SLOPE INTERCEPT AND CORRELATION COEFFICIENT

Parameter	Methanol: water
Slope	0.035
Intercept	0.005
R2	0.998

2.2.1.3 Precision

Precision of the method was studied by making three different concentrations, namely, 2, 6, and 10 µg/mL and relative standard deviation was calculated. Results of intraday precision are shown in Table 3 and interday in Table 4.

2.2.1.4 Accuracy

Accuracy was determined by spiking a known concentration of pure drug in a mixture of marketed formulation solutions. The recovery of drug in the presence of marketed formulation was found to be in between the predefined acceptance criteria. Results of accuracy were shown in Table 5.

2.2.2 Compatibility study of drug and polymers

The compatibility study for drug and polymer was conducted by exposing the physical mixture of drug and polymer to X-ray diffractometry (Philips PW-3710) and DSC (Pyris Diamond TG/DTA, Make-PerkinElmer). Results shown in Figure 2.1, 2.2, and 2.3 indicate that there is no interaction.

2.2.3 Formulation of transdermal patches with different polyme

A 3^2-randomized full factorial design was used in the present study. In this design, two independent factors were evaluated, each at three levels and experimental trials were performed for all nine possible combinations. The compositions of HPMC and ethyl cellulose were chosen as independent variables. F1 to F9 batches were prepared using the factorial design and were analyzed for thickness, flatness, folding endurance, tensile strength, moisture content, moisture uptake, and drug content.

The drug-free patches were prepared using polymers such as HPMC, Carbopol 934, ethyl cellulose, sodium lauryl sulfate, dimethyl sulfoxide, propylene glycol, polyethylene glycol, isopropyl myristate, methanol, and chloroform.

For the preparation of transdermal patches of LHCl were prepared using solvent evaporation method on aluminum foil. Accurately weighed quantity of 100 mg HPMC, 100 mg sodium lauryl sulfate and 400 mg ethyl cellulose were taken in a clean dry beaker. Solution of 30 mg LHCl was prepared by dissolving it in sufficient quantity of a mixture of methanol: chloroform. The solution was added to a beaker and mixed well.

Polymeric solution of remaining 70 mg of LHCl hydrochloride was prepared using 100 mg HPMC dissolved in chloroform and was kept for evaporation. Polymeric powder thus obtained was added to the beaker with constant stirring along with a small quantity of solvent. The gel-like formulation was obtained. It was poured on aluminum foil in Petri dish and kept in an oven at 37°C for 12 h.[13-18]

2.2.4 Characterization of transdermal patches [22-32]

The characterization of transdermal patches was done by evaluating parameters such as thickness, flatness, folding endurance, tensile strength, moisture content, moisture uptake, and drug content. Comparative results are mentioned in Table 6.[20,21]

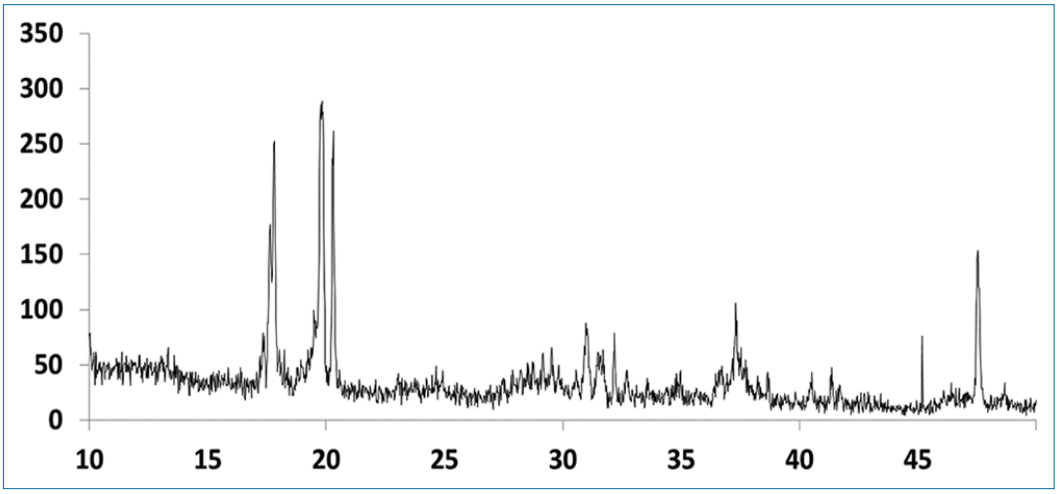
TABLE 3
RESULTS OF INTRADAY PRECISION

State	Concentration	% Concentration	% RSD
Morning	2	102	0.4
	6	105	
	10	94.3	
Afternoon	2	100.05	0.6
	6	109.1	
	10	90.1	
Evening	2	120.1	1.1
	6	118.4	
	10	114.1	

TABLE 4
RESULTS OF INTERDAY PRECISION

State	Concentration	% Concentration	% RSD
Morning	2	114.5	0.5
	6	115.02	
	10	101.14	
Afternoon	2	115.03	0.6
	6	119.08	
	10	98.04	
Evening	2	120.2	0.8
	6	118.1	
	10	96.03	

FIGURE 2.1: X-ray diffractometer of formulated patch



2.2.5 Thickness

Patch thickness was measured using digital micrometer screw gauge (Mitutoyo, Japan) at three different places and the mean value was calculated.

2.2.6 Folding endurance

Folding endurance of patches was determined by repeatedly folding a small strip of film (2 cm × 2 cm) at the same place till it broke. The number of time the film could be folded at the same place without breaking was the folding endurance value of that prepared transdermal film.

TABLE 5
RESULTS OF ACCURACY

Level of recovery	Amount added (mg)	Concentration recorded (mg)	% Recovery	% RSD
80	8	7.55	94.3	0.87
	8	7.48	93.5	
	8	7.74	96.7	
100	10	9.74	97.4	1.23
	10	9.65	96.5	
	10	10.22	102.2	
120	12	11.71	97.5	1.41
	12	12.4	103.3	
	12	11.85	98.7	

TABLE 6
RESULTS OF THICKNESS, FOLDING ENDURANCE, TENSILE STRENGTH

Batch code	Folding		Mean±SD		
	Tensile strength kg/cm2)		%	Thickness (mm)	% Drug
F1	177±3.2	0.528±0.007	41.2±0.015	0.1645±0.019	100.02±0.59
F2	179±5.2	0.535±0.009	38.8±0.014	0.1704±0.013	98.23±2.38
F3	170±3.8	0.520±0.015	37.1±0.012	0.1695±0.014	102.30±1.69
F4	170±3.8	0.548±0.013	40.2±0.013	0.2015±0.017	104.51±3.9
F5	177±3.2	0.551±0.016	39.6±0.017	0.1849±0.001	100.02±0.59
F6	175±1.2	0.540±0.005	35.8±0.012	0.1645±0.019	101.18±0.57
F7	172±1.8	0.542±0.007	39.2±0.013	0.1704±0.013	99.37±1.24
F8	175±1.2	0.537±0.002	28.9±0.015	0.1695±0.014	98.65±1.96
F9	170±3.8	0.525±0.010	30.1±0.015	0.2015±0.017	104.23±3.62

2.2.7 Tensile strength

The tensile strength was determined using a modified pulley system. The strip of the patch (2×1 cm^2) was cut and hold between the two clamps present on pulley system. Weights were increased gradually in pan. The force required to break the film was considered as a tensile strength and was calculated as kg/cm^2.

2.2.8 Percentage of moisture content

The films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 h. Films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated using formula and is presented in Table 7.

$$\text{Percentage of moisture content} = \frac{\text{Final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

TABLE 7
RESULT OF MOISTURE CONTENT

Batch no	% Moisture content
F1	5.20±1.81
F2	4.05±0.66
F3	4.25±0.86
F4	2.30±1.09
F5	2.78±0.61
F6	3.09±0.30
F7	2.87±0.52
F8	2.93±0.46
F9	2.50±0.29

2.2.9 Percentage of moisture uptake

The prepared patches were weighed individually and kept in a desiccator containing fused calcium chloride at room temperature for 24 h. After 24 h, the films were reweighed and determined the percentage moisture content from the below-mentioned formula and are presented in Table 8.

$$\text{Percentage of moisture content} = \frac{\text{Final weight} - \text{initial weight}}{\text{initial weight}} \times 100$$

TABLE 8
RESULTS OF % MOISTURE UPTAKE

S. No	% Moisture uptake
F1	10.60±0.63
F2	9.39±0.58
F3	11.54±1.57
F4	10.47±0.50
F5	9.09±0.88
F6	10.35±0.38
F7	10.25±0.28
F8	8.55±1.42
F9	9.55±0.42

2.2.10 Determination of drug content

A 5 cm^2 patch was cut into small pieces, put into a 100 ml phosphate buffer pH 7.4 and shaken continuously for 24 h. The whole solution was ultrasonicated for 5 min. The drug concentration was analyzed using ultraviolet spectrophotometer at a wavelength of 218 nm. The results are presented in Table 9.

TABLE 9
RESULTS OF DRUG CONTENT

Batch No.	Drug content
F1	100.02±0.59
F2	98.23±2.38
F3	102.30±1.69
F4	104.51±3.9
F5	97.05±3.56
F6	101.18±0.57
F7	99.37±1.24
F8	98.65±1.96
F9	104.23±3.62

FIGURE 3: Drug release profile of different formulation

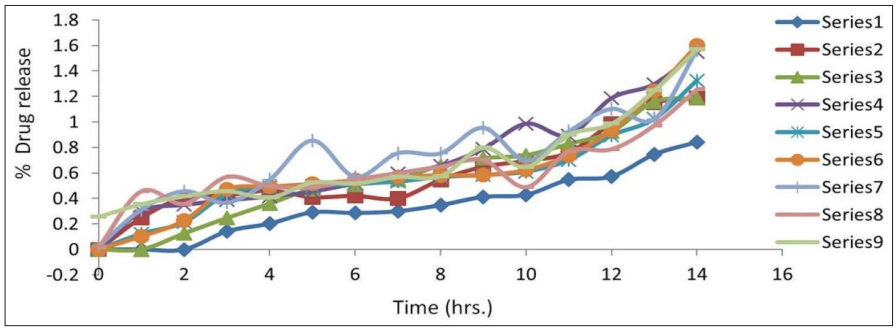


FIGURE 2.2: DSC results of formulated polymeric patch (without drug)

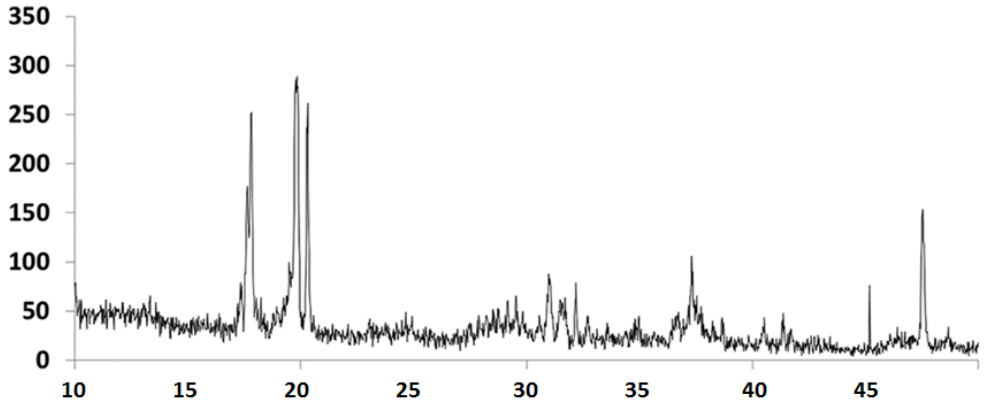
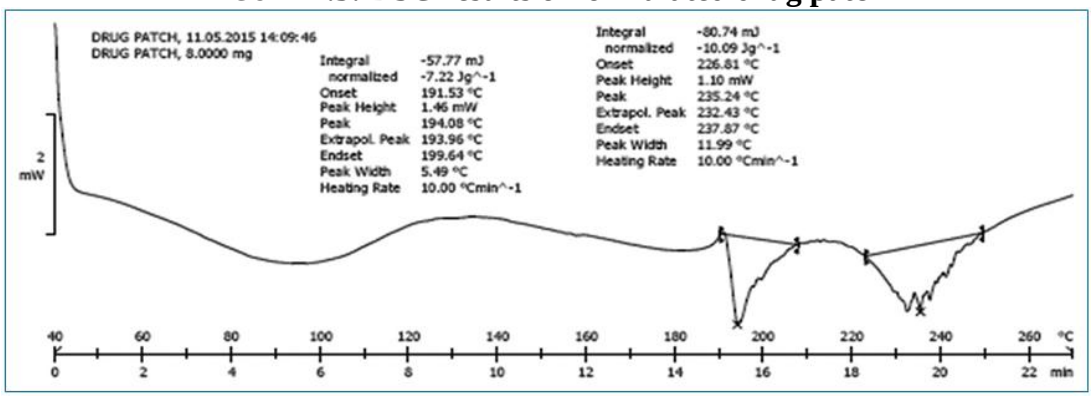


FIGURE 2.3: DSC results of formulated drug patch



2.2.11 In Vitro Diffusion Studies

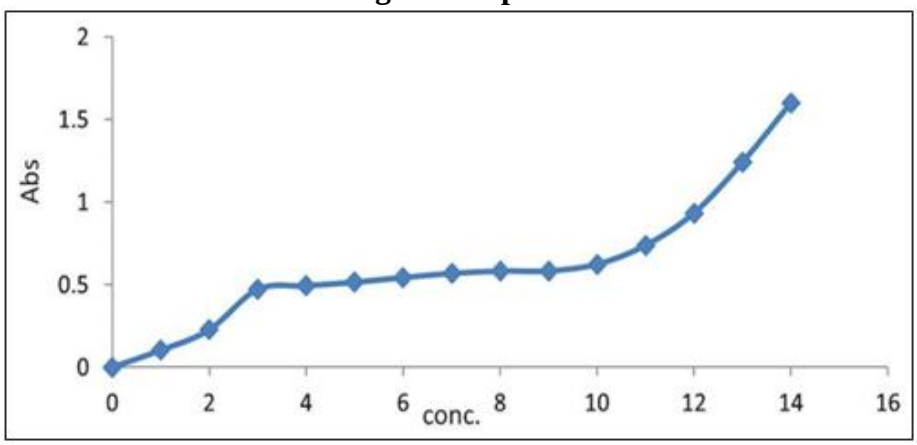
The diffusion studies were conducted to get an idea of permeation of drug through barrier from the transdermal systems. The Franz and Keshary Chien (K-C) type of horizontal diffusion cells with a receptor compartment capacity of 22 ml was utilized. The cellulose acetate membrane (pore size 0.45 µ) was mounted between the donor and receptor compartment of the diffusion cell. The transdermal film was placed on the cellulose acetate membrane and covered with aluminum foil.

The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a hot plate magnetic stirrer, and the solution in the receptor compartment was constantly stirred using magnetic beads, and the temperature was maintained at 32 ± 0.5°C. The diffusion study was carried out for 12 h, and 1 ml sample was withdrawn at an interval of 1 h. The samples were analyzed for drug content at 218 nm. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. Results are presented in Table 10 and Figure 3. The result of drug release from optimized formulation batch F6 has been presented separately in Table 10 and Figure 4.

TABLE 10
RESULT OF IN VITRO DRUG RELEASE

Time (h)	% Drug release
1	2.79
2	6.33
3	13.33
4	13.94
5	14.55
6	15.37
7	16.08
8	16.48
9	16.51
10	17.66
11	20.93
12	26.52
13	35.34
14	45.59

FIGURE 4: Drug release profile of ideal batch



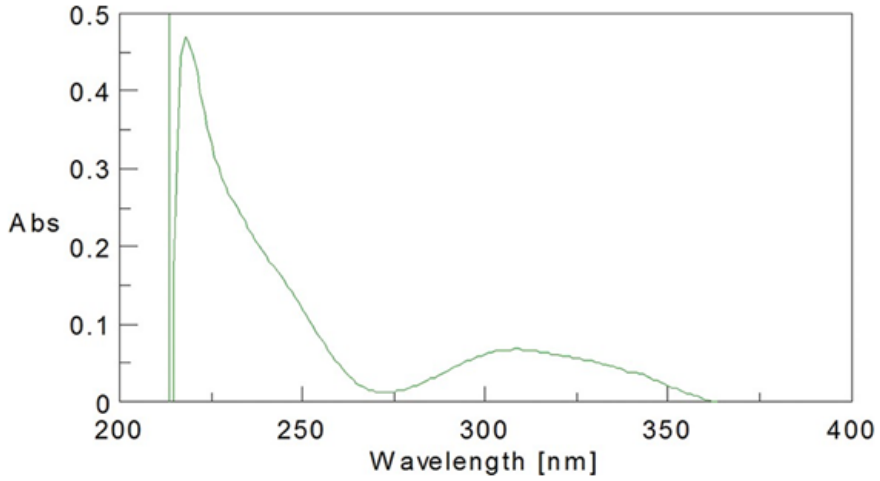
2.2.12 Stability Study

According to the ICH guidelines 257, the TDDS samples were stored at 40 ± 0.5°C and 75 ± 5% relative humidity (RH) for 3 months. The samples were withdrawn at 0, 30, 60, 90, and 180 days and analyzed for physicochemical parameters as well as drug diffusion. If a significant change occurs at these stress conditions, then the formulation should be tested at an intermediate condition, i.e. 30°C and 75% RH. The stability studies were carried out for F6 formulation which was optimized formulation.[19]

III. RESULT AND DISCUSSION

3.1 Determination of λ max

From fig. it was found that the λ max for labetalol hydrochloride in methanol: water system was found to be 218nm.



3.2 Calibration related result and discussion.

3.2.1 Linearity

TABLE 11
RESULTS OF LINEARITY

Concentration (µg/ml)	Absorbance
2	0.0762
4	0.1503
6	0.2233
8	0.2931
10	0.3502

Experimentally the linearity for labetalol hydrochloride in methanol: Water system at 218 nm was found to between 2-10 µg/ml.

3.2.2 Precision

3.2.2.1 Intraday Precision

TABLE 3.1
RESULTS OF INTRADAY PRECISION

State	Concentration	% Concentration	% RSD
Morning	2	102	0.4
	6	105	
	10	94.3	
Afternoon	2	100.05	0.6
	6	109.1	
	10	90.1	
Evening	2	120.1	1.1
	6	118.4	
	10	114.1	

3.2.2.2 Interday Precision

TABLE 3.2
RESULTS OF INTERDAY PRECISION

State	Concentration	% Concentration	% RSD
Morning	2	114.5	0.5
	6	115.02	
	10	101.14	
Afternoon	2	115.03	0.6
	6	119.08	
	10	98.04	
Evening	2	120.2	0.8
	6	118.1	
	10	96.03	

From the experimental procedure % RSD values for interday and intraday precision were found to be within limits.

3.2.2.3 Accuracy

TABLE 3.3
RESULTS OF ACCURACY

Level of recovery	Amount Added (mg)	Concentration recorded (mg)	Recovery %	RSD %
80	8	7.55	94.3	0.87
	8	7.48	93.5	
	8	7.74	96.7	
100	10	9.74	97.4	1.23
	10	9.65	96.5	
	10	10.22	102.2	
120	12	11.71	97.5	1.41
	12	12.4	103.3	
	12	11.85	98.7	

From experimental procedure the % recovery of drug in the developed formulation was found to be with in acceptance criteria on the basis of values of % RSD.

3.2.3 Characterization of transdermal films

3.2.3.1 Thickness

TABLE 3.4
RESULTS OF THICKNESS

Batch No.	Thickness	Batch No.	Thickness
F1	0.1645±0.019	F6	0.1910±0.007
F2	0.1704±0.013	F7	0.1712±0.012
F3	0.1695±0.014	F8	0.2135±0.029
F4	0.2015±0.017	F9	0.1862±0.002
F5	0.1849±0.001		

3.2.3.2 Folding endurance

TABLE 3.5
RESULTS OF FOLDING ENDURANCE

Batch No.	Folding endurance
F1	177±3.2
F2	179±5.2
F3	170±3.8
F4	170±3.8
F5	177±3.2
F6	175±1.2
F7	172±1.8
F8	175±1.2
F9	170±3.8

3.2.3.3 Tensile strength

TABLE 3.6
RESULTS OF TENSILE STRENGTH

Sr.No	Tensile strength kg/cm^2
F1	0.528 ± 0.007
F2	0.535
F3	0.520 ± 0.015
F4	0.548 ± 0.013
F5	0.551 ± 0.016
F6	0.540 ± 0.005
F7	0.542 ± 0.007
F8	0.537 ± 0.002
F9	0.525 ± 0.010

3.2.3.4 Percentage of moisture content

TABLE 3.7
RESULT OF MOISTURE CONTENT

Batch no	Moisture Content %	Batch No.	Moisture Content %
F1	5.20±1.81	F6	3.09±0.30
F2	4.05±0.66	F7	2.87±0.52
F3	4.25±0.86	F8	2.93±0.46
F4	2.30±1.09	F9	2.50±0.29
F5	2.78±0.61		

3.2.3.5 Percentage moisture uptake

TABLE 3.7
RESULT OF MOISTURE UPTAKE

Sr. No.	Moisture Uptake %	Sr. No.	Moisture Uptake %
F1	10.60±0.63	F6	10.35±0.38
F2	9.39±0.58	F7	10.25±0.28
F3	11.54±1.57	F8	8.55±1.42
F4	10.47±0.50	F9	9.55±0.42
F5	9.09±0.88		

3.2.4 Drug Content

3.2.4.1 Results of drug content

TABLE 3.8
RESULTS OF DRUG CONTENT

Batch No.	Drug Content	Batch No.	Drug Content
F1	100.02±0.59	F6	101.18±0.57
F2	98.23±2.38	F7	99.37±1.24
F3	102.30±1.69	F8	98.65±1.96
F4	104.51±3.9	F9	104.23±3.62
F5	97.05±3.56		

3.2.4.2 In-vitro drug release profile

TABLE 12
***IN VITRO* DRUG RELEASE PROFILE FOR F6 FORMULATION THE OPTIMIZED FORMULATION [19]**

Time (hrs)	Drug Release %
1	2.79
2	6.33
3	13.33
4	13.94
5	14.55
6	15.37
7	16.08
8	16.48
9	16.51
10	17.66
11	20.93
12	26.52
13	35.34
14	45.59

From the experimental procedure carried out for thickness folding endurance, tensile strength, percentage of moisture content, percentage of Moisture Uptake and determination of drug Content the values were found to be within acceptance criteria.

3.2.5 Stability testing

The present work of stability study was carried out for optimized formulation (F6) at 40 ± 0.5°C and 75 ± 5% RH for 1 month using programmable environmental test chamber (Remi, India). The sample was evaluated for drug content uniformity, and it was found to be 98.54%.

IV. DISCUSSION

A successful development and evaluation of transdermal patches of LHCl prepared by solvent evaporation method have been done. All the patches prepared were subjected to evaluation parameters such as thickness (0.1910±0.007), % moisture uptake (10.35±0.38), % moisture content (3.09±0.30), tensile strength (0.540±0.005), folding endurance (175±1.2), drug content (101.18±0.57), and *in-vitro* diffusion study and stability study. A successful analytical method was also developed for formulated preparation. On the basis of results of various tests carried out for F1 to F9 formulations, F6 was found to be optimized formulation.

V. CONCLUSION

The prepared TDDS of patches of LHCl using different grades of HPMC and ethyl cellulose has shown promising results for all the evaluated parameters. It can be concluded use of HPMC K100 and ethyl cellulose can be done successfully in preparation of sustained release matrix type of transdermal patches which can show greater patient compliance in treating hypertension successfully.

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